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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,579	03/30/2006	Lawrence Mayer	532552000701	3865

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
04/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,579	MAYER ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34 and 36-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34 and 36-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-31-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 2-25-08 is acknowledged.

Claims included in the prosecution are 33-34 and 36-42.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 33-34 and 36-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/62235 in view of WO 95/15154, Rahman (7,122,553) and in further combination with Vaage et al (International J. of cancer (1993), Mayer (6,083,530) by themselves or in combination.

WO 01 teaches a method of administration of compositions containing camptothecin and a pyrimidine derivative having a therapeutic synergy in the treatment of cancer. The agents are separately administered. The camptothecin derivatives include Irinotecan and others. The pyrimidine derivatives include uracil (abstract, page 1 and examples).

What is lacking in WO is the teaching of the liposomes as the delivery vehicles for the camptothecin and the pyrimidine derivative.

WO 95 discloses liposomal formulations containing FudR teaches for the

treatment of hepatic metastases (abstract and page 3).

Rahman teaches liposomal compositions containing Irinotecan for increased therapeutic efficacy and reduced toxicity (abstract, col. 2, 4 and claims).

Vaage et al teach compositions containing liposomes (vehicles) and encapsulated therein two therapeutic agents, vincristine and doxorubicin. The therapeutic agents are in two separate liposome formulations. The liposome sizes are 80 nm. According to Vaage, the liposome formulations are significantly more effective than the free drugs. (Abstract, Materials and Methods and results). Vaage in addition teaches that a ~number or studies in animal models have shown that the therapeutic activities of anti-cancer drugs can be increased and prolonged and toxic effects reduced when they are encapsulated in liposomes (page 959, col. 1).

Mayer while disclosing liposomal formulations containing antineoplastic agents teaches that drug cocktails containing two or populations of liposomes containing different antineoplastic agents can be prepared and administered for greater therapeutic efficacy (abstract and col. 9, lines 20-25).

To administer the camptothecin and pyrimidine derivatives of WO 01 in liposomes would have been obvious to one of ordinary skill in the art since the references of WO 95 and Rahman teach the increased therapeutic efficacy of these agents when encapsulated in liposomes. One of ordinary skill in the art would be motivated to encapsulate these agents in separate liposomes and administer since the reference of Vaage shows that one can administer them together but in separate

liposome formulations and that of Mayer teaches that two populations of liposomes containing two different antineoplastic agents can be administered for greater therapeutic efficacy.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that WO discloses separate administration of camptothecin and a pyrimidine derivative in a manner in which therapeutic synergy is achieved. Applicant notes that not all of the pyrimidine derivatives are fluoropyrimidines, *e.g.,* uracil, and the exemplified pyrimidine derivative, capecitabine, which is no longer a fluoropyrimidine as it lacks a pyrimidine ring and points out to page 6. These arguments are not persuasive. If the purpose in WO is to administer these drugs separately, then the inventors would not have claimed a single composition containing both drugs. This is clearly evident in the summary and in the claims. Furthermore, the co administration of the two compounds is clearly evident from Example 2. Applicant argues that WO does not even suggest compositions where the two drugs are present at a non-antagonist ratio. According to applicant, though WO 01 says that it is looking for synergy, the synergy of WO 01 is quite different from the additivity or synergy required in the present application. Applicant points out to page 4, line 15 in WO which apparently defines synergy as, "A combination manifests therapeutic synergy if it is therapeutically superior to one or the other of the constituents used at its optimum dose". This argument is not persuasive since according to instant claims the non-antagonist ratios of the drugs are within the liposomes and not as free drugs. Applicant has not shown that the drugs in the ratios taught by WO when encapsulated within the liposomes would not provide a

synergistic effect. Furthermore, applicant themselves have not defined in the specification as to what synergy means when the drug combination is administered to a cancer patients and ***how it can be evaluated in vivo.*** With regard to applicant's arguments that WO 01 does not have any disclosure that any administered synergistic ratio is maintained for at least an hour, the examiner points out that the rejection is made on the combination of references and applicant has not shown that the amounts of the anti-neoplastic agents disclosed by WO do not maintain a synergistic ratios when encapsulated within the liposomes and administered to humans. Furthermore, a careful examination of the specification indicates the use of liposomes made from specific phospholipids and applicant has presented no evidence to indicate that liposomes made of any phospholipid would maintain the same synergistic ratio for 1 hour. The examiner is perplexed with applicant's arguments that capecitabine is not a fluoropyrimidine. Capecitabine is a fluoropyrimidine carbamate as evident from page 5, lines 22-26 of WO and the structure on page 6 clearly shows fluorine and the pyrimidine ring.

Applicant argues that the combination of WO 95 with WO 01 fails to suggest the invention because it fails to require that the liposomes be carriers for both drugs and that the liposome be such that the synergistic ratio administered be maintained for at least one hour in the subject. This argument is not persuasive since WO is combined for its teachings of the encapsulation of FudR which applicants do not contend. Although WO 95 does not teach the combination of camptothecins and fluoropyrimidines, it does teach encapsulation of FudR and that liposomal FudR is capable of providing a synergy with

drugs such as leucovorin and as pointed out above, WO 01 teaches the claimed combination.

Applicant argues that even if Rahman is combined with the forgoing two documents, it fails to teach the essential feature of the invention – that a synergistic ratio be administered for at least one hour in the blood of a subject. This argument is not persuasive since Rahman is combined for its teachings of the knowledge in the art of the encapsulation of camptothecins in liposomes for enhanced efficacy and the combination of the drugs is taught by WO 01.

Applicant's arguments regarding Vaage are not persuasive. Vaage is combined for the knowledge in the art of the administration of two populations of liposomes containing anti-neoplastic agents. The differences argued by applicant are applicable for the combination of Doxil and VCR taught by Vaage; however, WO 01 clearly teaches that the combination of camptothecins and fluoropyrimidines can be successfully administered and therefore, one of ordinary skill in the art would be motivated to administer two populations of liposomes and not expect the deleterious effects observed when Doxil and VCR are administered together. With regard to synergism argued once again by applicant, the examiner points out that applicant defines synergism based on an in vitro model, but does not explain how one can determine an effect is additive or synergistic in terms of actual treatment of a subject having cancer, when two drugs are administered. Instant claims are drawn to a method of delivery to obtain a synergistic therapeutic effective amount.

Applicant argues that there is nothing in Mayer that would imply that the ratio of the components in the cocktails be set so as to be synergistic in the first place, much less any suggestion that the liposomal formulations be adjusted to control the pharmacokinetics so that the ratio is maintained. These arguments are not persuasive since Mayer is combined for its teachings of greater efficacy of the combination of drugs when administered in liposomes. Applicant's arguments regarding synergism have already been addressed by the examiner.

Note: 'by themselves or in combination' pertain to Vaage et al (International J. of cancer (1993), Mayer (6,083,530).

In view of the terminal disclaimers, the double patenting rejections are withdrawn.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK